COMPREHENSIVE TABLE OF CONTENTS
HEADINGS AND HIERARCHY

Comprehensive Table of Contents Headings and Hierarchy

❖ Module 1 Administrative information

- ***Forms***
  - Application form: FDA form 1571
  - Application form: FDA form 356h
  - User fee cover sheet: FDA form 3397
  - Annual report transmittal: FDA form 2252
  - Advertisements and promotional labeling transmittal: FDA form 2253
  - FDA form 2567
- ***Cover letters***
- ***Administrative information***
  - Contact/sponsor/Applicant information
    - **Change of address or corporate name**
    - **Change in contact/agent**
    - **Change in sponsor**
    - **Transfer of obligation**
    - **Change in ownership of an application**
  - Field copy certification
  - Debarment certification
  - Financial certification and disclosure
  - Patent and exclusivity
    - **Patent information**

- **Patent certification**
- **Exclusivity request**

➢ ***References***

- Letter of authorization
- Statement of right of reference
- List of authorized persons to incorporate by reference
- Cross reference to other applications

➢ ***Application status***

- Withdrawal request
- Inactivation request
- Reactivation request
- Reinstatement request
- Withdrawal of an unapproved NDA
- Withdrawal of listed drug
- Request for withdrawal of application approval

➢ ***Meetings***

- Meeting request
- Meeting background materials
- Correspondence regarding meetings

➢ ***Fast track***

- Fast track designation request
- Fast track designation withdrawal request

- Rolling review request

- ***Special protocol assessment request***
  - Clinical study
  - Carcinogenicity study
  - Stability study

- ***Pediatric administrative information***
  - Request for waiver of pediatric studies
  - Request for deferral of pediatric studies
  - Request for pediatric exclusivity determination
  - Proposed pediatric study request and amendments
  - Proposal for written agreement
  - Other correspondence regarding pediatric exclusivity or study plans

- ***Dispute resolution***
  - Request for dispute resolution
  - Correspondence related to dispute resolution

- ***Information amendment: Information not covered under modules 2 to 5***
  - Quality information amendment
  - Safety information amendment
  - Efficacy information amendment
  - Multiple module information amendments

- ***Other correspondence***
  - Pre IND correspondence

- Request to charge
- Notification of charging under treatment IND
- Request for comments and advice on an IND
- Request for a waiver
- Exemption from informed consent for emergency research
- Public disclosure statement for emergency care research
- Correspondence regarding emergency care research
- Notification of discontinuation of clinical trial
- Generic drug enforcement act statement
- Basis for submission statement
- Comparison of generic drug and reference listed drug
- Request for waiver for in vivo studies
- Environmental analysis
- Request for waiver of in vivo bioavailability studies
- Field alert reports

➢ ***Annual report***

- Summary for nonclinical studies
- Summary of clinical pharmacology information
- Summary of safety information
- Summary of labeling changes
- Summary of manufacturing changes
- Summary of microbiological changes
- Summary of other significant new information

- Individual study information
- General investigational plan
- Foreign marketing history
- Distribution data
- Status of postmarketing study commitments
- Status of other postmarketing studies
- Log of outstanding regulatory business

➢ ***Labeling***

- Draft labeling
  - **Draft carton and container labels**
  - **Annotated draft labeling text**
  - **Draft labeling text**
  - **Label comprehension studies**
  - **Labeling history**
- Final labeling
  - **Final carton or container labels**
  - **Final package insert (package inserts, patient information, Medication guides)**
  - **Final labeling text**
- Listed Drug Labeling
  - **Annotated comparison with listed drug**
  - **Approved labeling text for listed drug**
  - **Labeling text for reference listed drug**

- Investigational drug labeling
  - **Investigational brochure**
  - **Investigational drug labeling**
- Foreign labeling

➢ ***Promotional material***

➢ ***Risk management plans***

❖ Module 2 Summaries

➢ ***Table of contents***

➢ ***Introduction to summary***

➢ ***Quality overall summary***

- Drug Substance [name, manufacturer]
  - General information
  - Manufacture
  - Characterization
  - Control of drug substance
  - Reference standards or materials
  - Container closure system
  - Stability
- Drug Product [name, dosage form]
  - Description and composition of the drug product
  - Pharmaceutical development
  - Manufacture

        - Control of excipients
        - Control for drug product
        - Reference standards or materials
        - Container closure system
        - Stability
    - Appendices
        - Facilities and equipment
        - Adventitious agents safety evaluation
        - Excipients
    - Regional information
- ***Nonclinical overview***
- ***Clinical overview***
- ***Nonclinical written and tabulated summaries***
    - Introduction
    - Pharmacology written summary
    - Pharmacology tabulated summary
    - Pharmacokinetic written summary
    - Pharmacokinetic tabulated summary
    - Toxicology written summary
    - Toxicology tabulated summary
- ***Clinical summary***

- Summary of Biopharmaceutic Studies and Associated Analytical Methods
- Summary of Clinical Pharmacology studies
- Summary of Clinical Efficacy [indication]
- Summary of Clinical Safety
- References
- Synopses of individual studies

❖ Module 3 Quality

➢ *Table of contents*

➢ *Body of data*

- Drug Substance [name, manufacturer]

  - **General Information**
    - ♦ Nomenclature
    - ♦ Structure
    - ♦ General properties
  - **Manufacture**
    - ♦ Manufacturer(s)
    - ♦ Description of Manufacturing Process and Process Controls
    - ♦ Control of Materials
    - ♦ Controls of Critical Steps and Intermediates
    - ♦ Process Validation and/or Evaluation
    - ♦ Manufacturing Process Development
  - **Characterization**
    - ♦ Elucidation of Structure and other Characteristics
    - ♦ Impurities
  - **Control of Drug Substance**
    - ♦ Specification

- Analytical Procedures
- Validation of Analytical Procedures
- Batch Analyses
- Justification of Specification

- **Reference Standards or Materials**
- **Container Closure Systems**
- **Stability**
  - Stability Summary and Conclusions
  - Post Approval Stability Protocol and Stability Commitment
  - Stability Data

- Drug product [name, dosage form, manufacturer]
  - **Description and Composition of the Drug Product**
  - **Pharmaceutical Development**
    - Components of the Drug Product
    - Drug Substance
    - Excipients
    - Drug Product
    - Formulation Development
    - Overages
    - Physicochemical and Biological Properties
    - Manufacturing Process Development
    - Container Closure System
    - Microbiological Attributes
    - Compatibility
  - **Manufacture**
    - Manufacturer(s)
    - Batch Formula
    - Description of Manufacturing Process and Process Controls
    - Controls of Critical Steps and Intermediates
    - Process Validation and/or Evaluation

- **Control of Excipients**
  - Specification(s)
  - Analytical Procedures
  - Validation of Analytical Procedures
  - Justification of Specifications
  - Excipients of Human or Animal Origin
  - Novel Excipients
- **Control of Drug Product**
  - Specification(s)
  - Analytical Procedures
  - Validation of Analytical Procedures
  - Batch Analyses
  - Characterization of Impurities
  - Justification of Specification(s)
- **Reference Standards or Materials**
- **Container Closure System**
- **Stability**
  - Stability Summary and Conclusion
  - Post-approval Stability Protocol and Stability Commitment
  - Stability Data

➢ ***Appendices***

- **Facilities and Equipment [name, manufacturer]**
- **Adventitious Agents Safety Evaluation [name, dosage form, manufacturer]**
- **Excipients**

- ***Regional Information***
  - **Executed Batch Records**
  - **Method Validation Package**
  - **Comparability Protocols**
- ***Literature references***

❖ Module 4 Safety

- ***Table of contents***
- ***Study reports***
  - Pharmacology
    - **Primary pharmacodynamics**
      - Study report [identification number] and related information
        - *Legacy study report*
        - *Synopsis*
        - *Study report body*
        - *Protocol and amendments*
        - *Signatures of principal or coordinating investigator(s)*
        - *Audit certifications and reports*
        - *Documentation of statistical methods (E3 16.1.9) and interim analysis plans*
        - *Documentation of inter laboratory standardization methods of quality assurance procedures if used (E3 16.1.10)*
        - *Publications based on the study*
        - *Important publications referenced in the report (E3 16.1.12)*
        - *Compliance and/or drug concentration data (E3 16.2.5)*
        - *Individual subject data listings (E3 16.4)*
          - Data tabulation
            - *Data tabulation datasets*
            - *Data definitions*
          - Data listing datasets
            - *Data listing datasets*
            - *Data definitions*
          - Analysis datasets
            - *Analysis datasets*
            - *Analysis programs*
            - *Data definitions*
          - IND safety reports

- **Secondary pharmacodynamics**
  - Study report [identification number] and related information
    - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for headings*
- **Safety pharmacology**
  - Study report [identification number] and related information
    - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*
- **Pharmacodynamic drug interactions**
  - Study report [identification number] and related information
    - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*

▪ Pharmacokinetics

- **Analytical methods and validation reports**
  - Study report [identification number] and related information
    - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*
- **Absorption**
  - Study report [identification number] and related information
    - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*
- **Distribution**
  - Study report [identification number] and related information
    - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*
- **Metabolism**
  - Study report [identification number] and related information
    - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*
- **Excretion**
  - Study report [identification number] and related information
    - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*

- **Pharmacokinetic drug interactions**
  - Study report [identification number] and related information
    - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*
    - *Statement of QA differences*
- **Other pharmacokinetic studies**
  - Study report [identification number] and related information
    - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*

- Toxicology
  - **Single dose toxicity [Species and dose]**
    - Study report [identification number] and related information
      - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*
  - **Repeat dose toxicity**
    - [Species, route, duration]
      - *Study report [identification number] and related information*
        - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading
  - **Genotoxicity**
    - In vitro
      - *Study report [identification number] and related information*
        - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading
    - In vivo
      - *Study report [identification number] and related information*
        - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading
  - **Carcinogenicity**
    - Long term studies [Species]
      - Study report [identification number] and related information
        - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*
    - Short or medium term studies
      - *Study report [identification number] and related information*
        - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading
    - Other studies

- *Study report [identification number] and related information*
  - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading

- **Reproductive and developmental toxicity**

  - Fertility and early embryonic development
    - *Study report [identification number] and related information*
      - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading
  - Embryofetal development
    - *Study report [identification number] and related information*
      - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading
  - Prenatal and postnatal development, including maternal function
    - *Study report [identification number] and related information*
      - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading
  - Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
    - *Study report [identification number] and related information*
      - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading

- **Local tolerance**

  - Study report [identification number] and related information
    - *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*

- **Other toxicity studies**

  - Antigenicity
    - *Study report [identification number] and related information*
      - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading
  - Immunotoxicity
    - *Study report [identification number] and related information*
      - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading
  - Mechanistic studies
    - *Study report [identification number] and related information*
      - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading
  - Dependence
    - *Study report [identification number] and related information*
      - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading
  - Metabolites

- *Study report [identification number] and related information*
  - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading

♦ Impurities
- *Study report [identification number] and related information*
  - See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading

- **Other**

♦ Study report [identification number] and related information
- *See 4.2.1.1 Primary pharmacodynamics Study report and related information for heading*

➢ ***Literature references***

❖ Module 5 Efficacy

➢ ***Table of contents***

➢ ***Tabular listing of all clinical studies***

➢ ***Clinical study reports and related information***

▪ Reports of biopharmaceutic studies

- **Bioavailability (BA) Study reports and related information**

♦ Study report [identification] and related information
- *Legacy study report*
- *Synopsis (E3 2)*
- *Study report (E3 1, 3 to 15)*
- *Protocol and amendments (E3 16.1.1)*
- *Sample case report form (E3 16.1.2)*
- *List of IECs or IRBs (E3 16.1.3) and consent forms*
- *List and description of investigators (E3 16.1.4) and sites*
- *Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer (E3 16.1.5)*
- *Listing of patients receiving test drug(s) from specified batch (E3 16.1.6)*
- *Randomisations scheme (E3 16.1.7)*
- *Audit certificates (E3 16.1.8) and reports*
- *Documentation of statistical methods (E3 16.1.9) and interim analysis plans*
- *Documentation of inter laboratory standardization methods of quality assurance procedures if used (E3 16.1.10)*
- *Publications based on the study (E3 16.1.11)*
- *Important publications referenced in the report (E3 16.1.12)*
- *Discontinued patients (E3 16.2.1)*

- *Protocol deviations (E3 16.2.2)*
- *Patients excluded from the efficacy analysis (E3 16.2.3)*
- *Demographic data (E3 16.2.4)*
- *Compliance and/or drug concentration data (E3 16.2.5)*
- *Individual efficacy response data (E3 16.2.6)*
- *Adverse event listings (E3 16.2.7)*
- *Listing of individual laboratory measurements by patient (E3 16.2.8)*
- *Case report forms (E3 16.3)*
  - Site [identifier]
- *Individual patient data listings (E3 16.4)*
  - Data tabulation
    - *Data tabulation datasets*
    - *Data definitions*
  - Data listing datasets
    - *Data listing datasets*
    - *Data definitions*
  - Analysis datasets
    - *Analysis datasets*
    - *Analysis programs*
    - *Data definitions*
  - Annotated CRF
  - Subject profiles
  - IND safety reports

- **Comparative BA and bioequivalence (BE) Study reports and related information**

  - Study report [identification] and related information
    - *See example under bioavailability (BA) Study reports and related information for headings*

- **In Vitro - in Vivo correlation Study reports and related information**

  - Study report [identification] and related information
    - *See example under bioavailability (BA) Study reports and related information for headings*

- **Reports of bioanalytical and analytical methods for human studies**

  - Study report [identification] and related information
    - *See example under bioavailability (BA) Study reports and related information for headings*

- Reports of studies pertinent to pharmacokinetics using human biomaterials

  - **Plasma protein binding Study reports and related information**

    - Study report [identification] and related information

- *See example under bioavailability (BA) Study reports and related information for headings*

- **Reports of hepatic metabolism and drug interaction studies**

  - Study report [identification] and related information
    - *See example under bioavailability (BA) Study reports and related information for headings*

- **Reports of studies using other human biomaterials**

  - Study report [identification] and related information
    - *See example under bioavailability (BA) Study reports and related information for headings*

- Reports of human pharmacokinetic (PK) studies

  - **Healthy subject PK and initial tolerability Study reports and related information**

    - Study report [identification] and related information
      - *See example under bioavailability (BA) Study reports and related information for headings*

  - **Patient PK and initial tolerability Study reports and related information**

    - Study report [identification] and related information
      - *See example under bioavailability (BA) Study reports and related information for headings*

  - **Intrinsic factor PK Study reports and related information**

    - Study report [identification] and related information
      - *See example under bioavailability (BA) Study reports and related information for headings*

  - **Extrinsic factor Study reports and related information**

    - Study report [identification] and related information
      - *See example under bioavailability (BA) Study reports and related information for headings*

  - **Population PK Study reports and related information**

    - Study report [identification] and related information
      - *See example under bioavailability (BA) Study reports and related information for headings*

- Reports of human pharmacodynamic (PD) studies

  - **Healthy subject PD and PK/PD Study reports and related information**

    - Study report [identification] and related information
      - *See example under bioavailability (BA) Study reports and related information for headings*

  - **Patient PD and PK/PD Study reports and related information**

    - Study report [identification] and related information
      - *See example under bioavailability (BA) Study reports and related information for headings*

- Reports of efficacy and safety studies [Indication]

  - **Study reports and related information of controlled clinical studies pertinent to the claimed indication**

    - Placebo control
      - *Study report [identification] and related information*
        - See example under bioavailability (BA) Study reports and related information for headings

    - No treatment control
      - *Study report [identification] and related information*
        - See example under bioavailability (BA) Study reports and related information for headings

    - Dose response without placebo
      - *Study report [identification] and related information*
        - See example under bioavailability (BA) Study reports and related information for headings

    - Act*i*ve response without placebo
      - *Study report [identification] and related information*
        - See example under bioavailability (BA) Study reports and related information for headings

    - External (historical) control
      - *Study report [identification] and related information*
        - See example under bioavailability (BA) Study reports and related information for headings

  - **Study reports and related information of uncontrolled clinical studies**

    - Study report [identification] and related information
      - *See example under bioavailability (BA) Study reports and related information for headings*

- **Reports of analyses of data from more than one study**

  - Integrated analysis of safety
    - *Integrated summary of safety*
    - *Analysis datasets*
    - *Analysis programs*
  - Integrated analysis of efficacy
    - *Integrated summary of efficacy*
    - *Analysis datasets*
    - *Analysis programs*
  - Summary and update of safety information
  - Other analyses of data from more than one study

- **Other Study reports and related information**

  - Antibacterial reports
    - *In vitro study reports*
      - Antimicrobial Spectrum of Activity
      - Mechanism(s) of Action
      - Intracellular Antimicrobial Concentration Assessment
      - Mechanism of resistance studies
      - Susceptibility Test Method(s) and Methods for detection of Resistance Organisms
        - *Quality Control Parameters*
        - *Development of Interpretative Criteria and Quality Control Parameters for MIC Testing*
        - *Development of Interpretative Criteria and Quality Control Parameters for Disk Diffusion Testing*
        - *Resolving Differences between the FDA and Other Standard Setting Organizations*
      - Antimicrobial Interactions and Fixed Combination Studies
      - Miscellaneous
    - *Animal and human study reports*
      - Animal therapeutic and pharmacologic studies
      - Human pharmacology studies
        - *Pharmacokinetics*
        - *Pharmacodynamics*
    - *Provisional Interpretative Criteria*
    - *Correlation of Provisional Interpretative Criteria with Clinical Outcome*
      - Susceptibility Test Quality Control Data
      - Establishment of Breakpoints for Use in Labeling
      - Microbiology Subsection of the Package Insert Submitted in an NDA
        - *New Molecular Entities*
        - *Approved Drug Products*
  - Special pathogens (e.g., fungi, parasites, mycobacteria) and immune modulator reports
    - *In vitro study reports*
      - Mechanism of action
      - Activity
      - Drug resistance
      - Cross resistance

        - Effect of drug combinations on activity
        - Immunologic effects
        - other
    - *Animal study reports*
        - Mechanism of action
        - Activity
        - Drug resistance
        - Cross resistance
        - Effect of drug combinations on activity
        - Immunologic effects
        - other
    - *Clinical study reports*
        - Standardized methods
        - Non standardizes methods
        - Susceptibility criteria
        - Efficacy studies
        - Resistance/Cross resistance
        - other

- Antiviral reports
    - *In vitro study reports*
        - Study report [identification] and related information
            - *Study report*
            - *In vitro data*
    - *Animal model(s) study reports*
        - Study report [identification] and related information
            - *Study report*
            - *Animal model(s) data*
    - *Clinical) study reports*
        - Study report [identification] and related information
            - *Study report*
            - *Clinical in vivo data*
                - ***Viral load***
                - ***Resistance***
                - ***Other***
            - *In vivo (clinical) assays*
                - ***Viral load***
                - ***Genotype***
                - ***Phenotype***
                - ***Other***

- Other study reports

- Reports of postmarketing experience

    - **Postmarketing periodic adverse event drug experience report**

description

- ***Literature references***